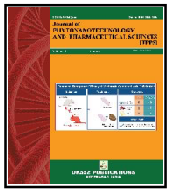
Journal of Phytonanotechnology and Pharmaceutical Sciences 5(4): 57-61, 2025

Online ISSN:2583-0376

http://jpps.ukaazpublications.com

DOI: http://dx.doi.org/10.54085/jpps.2025.5.4.7

Journal of Phytonanotechnology and Pharmaceutical Sciences



Original Article : Open Access

Comparative evaluation of saxagliptin alone and in combination with caffeic acid in STZ-induced diabetes in rats

Mohd Muzahid*, Badruddeen◆, Mohammad Irfan Khan**, Juber Akhtar**, Anas Islam**, Mohammad Ahmad**, Mohd Muazzam Khan**, Usama Ahmad**, Mohd Munazir*** and Rabiya Ahsan******

** Poineer Institute of Pharmacy, Bareilly-243126, Uttar Pradesh, India*

*** Department of Pharmacy, Faculty of Pharmacy, Integral University, Lucknow-226026, Uttar Pradesh, India*

**** Department of Pharmacy, Mohammad Ali Jauhar University, Rampur-244901, Uttar Pradesh, India*

***** Central Institute of Pharmacy, Hygia Group of Institution Lucknow-226013, Uttar Pradesh, India*

Article Info

Article history

Received 20 October 2025

Revised 28 November 2025

Accepted 29 November 2025

Published Online 30 December 2025

Keywords

Saxagliptin

Caffeic acid

Streptozotocin

Diabetes

Oxidative stress

Antioxidants

Pancreatic tissue

Abstract

The present study investigated the antidiabetic efficacy of saxagliptin alone and in combination with caffeic acid in streptozotocin (STZ)-induced diabetic rats. Adult male Sprague Dawley rats were divided into five groups: normal control, diabetic control, saxagliptin (10 mg/kg), caffeic acid (40 mg/kg), and saxagliptin (5 mg/kg) + caffeic acid (40 mg/kg). Diabetes was induced by intraperitoneal injection of STZ (65 mg/kg) followed by nicotinamide (110 mg/kg). After 15 days of treatment, blood glucose levels, oral glucose tolerance, body weight changes, total protein levels, and antioxidant status in pancreatic tissue were evaluated. The combination of saxagliptin and caffeic acid significantly decreased blood glucose levels, improved oral glucose tolerance, and increased body weight compared to saxagliptin alone. Additionally, the combination treatment significantly increased total protein levels and enhanced antioxidant status in pancreatic tissue, as evidenced by increased levels of superoxide dismutase, glutathione, and catalase, and decreased levels of malondialdehyde. These findings suggest that the combination of saxagliptin and caffeic acid exerts superior antidiabetic effects compared to saxagliptin alone, possibly through the mitigation of oxidative stress in pancreatic tissue. The results provide evidence for the potential therapeutic benefits of combining saxagliptin with caffeic acid in the management of type 2 diabetes mellitus.

1. Introduction

Diabetes mellitus (DM) is likely among the most ancient diseases known to humanity, with its first mention appearing in an Egyptian manuscript approximately 3000 years ago. The differentiation between type 1 and type 2 DM was clearly established in 1936. In 1988, type 2 DM was identified as a part of metabolic syndrome. Previously referred to as non-insulin dependent DM, type 2 DM is the most prevalent form of the disease, marked by high blood sugar levels, insulin resistance, and a relative lack of insulin. This type of diabetes arises from a combination of genetic, environmental, and behavioral risk factors (Hashim *et al.,* 2024; Hashim *et al.,* 2023). Various therapeutic approaches are currently available to manage this chronic metabolic condition, including stimulating the body's own insulin production, enhancing insulin effectiveness in target tissues, inhibiting the breakdown of dietary starches and lipids, and using oral hypoglycemic agents. STZ functions as an antimicrobial agent and also serves as a chemotherapeutic alkylating compound. It selectively accumulates in pancreatic β-cells through the GLUT2 glucose transporter, leading to β-cell necrosis and subsequently inhibiting insulin secretion (Shoaib *et al.,* 2020).

Corresponding author: Dr. Badruddeen

Professor, Faculty of Pharmacy, Integral University, Lucknow-226026, Uttar Pradesh, India

E-mail: badarmiracle@gmail.com

Tel.: +91-9918196188

Antioxidants, often referred to as "free radical scavengers," are compounds that can prevent or reduce cellular damage caused by free radicals. These free radicals are unstable molecules generated as by-products during various metabolic activities in the body. When there is an imbalance between the body's antioxidant defenses and the production of free radicals, a condition known as "oxidative stress" arises. Free radicals can harm cells, DNA, and lipids, leading to numerous disorders such as diabetes and neurodegenerative diseases (Singh *et al.,* 2024). Although, the body's natural antioxidants are generally adequate to neutralize free radicals produced during metabolic processes, they can sometimes become insufficient, necessitating the intake of external antioxidants. Sources of antioxidants include beta-carotene, and vitamins A, E (fat-soluble), and C (water-soluble). The mitochondrion is recognized as a primary source of reactive oxygen species (ROS) production, with mitochondria being the main site for superoxide (O_2-) generation. Superoxide dismutase converts superoxide into oxygen (O_2), while catalase and glutathione peroxidases transform hydrogen peroxide (H_2O_2) into water (H_2O). These enzymes are crucial in preventing oxidative stress (Singh *et al.,* 2024).

Polyphenolic compounds represent a varied class of naturally occurring substances characterized by multiple phenolic groups. These compounds are capable of effectively neutralizing free radicals, absorbing light in the ultraviolet (UV) spectrum (100-400 nm), and binding with transition metals, thereby preventing ongoing oxidative damage and the formation of unpleasant odors and tastes. They are

typically found in higher plants and exhibit a wide range of biological activities (Vuolo *et al.,* 2019; Yusuf *et al.,* 2019).

Saxagliptin, a reversible and competitive inhibitor of dipeptidyl peptidase-4, has recently been approved for managing T2DM. It functions by inhibiting the breakdown of glucagon-like peptide-1, thereby enhancing insulin secretion and reducing glucagon release. The inhibition of dipeptidyl peptidase 4 (DPP4) represents a novel and promising approach for treating type 2 diabetes. DPP4 is a proline-specific serine protease enzyme that swiftly degrades incretin hormones, such as gastric inhibitory polypeptide and glucagon-like peptide-1 (Boulton, 2017). Incretins play a crucial role in regulating both fasting and postprandial plasma glucose levels by promoting insulin secretion, supporting β-cell mass, and suppressing glucagon production by α-cells to decrease hepatic glucose production. DPP4 inhibitors improve glucose homeostasis by preventing the degradation of these incretins (Deacon, 2018). This study aimed to investigate the effects of saxagliptin combined with caffeic acid on STZ-induced diabetic rats.

2. Materials and Methods

2.1 Drugs and chemicals

The entire chemicals which were used are of analytical grade, and they are listed below: Streptozotocin (STZ), saxagliptin, caffeic acid, nicotinamide, ethanol, formaldehyde, diethyl ether and liquid gold total protein kit all chemicals were purchased by Sigma Aldrich, AstraZeneca, Autospan and Merck.

2.2 Animal

Adult male Sprague Dawley rats, weighing between 150 and 200 g, were obtained from the Central Drug Research Institute (CDRI) in Lucknow and housed at the Animal House Facility of the Faculty of Pharmacy, Integral University, Lucknow. The rats were placed in polypropylene cages, with five animals per cage. The laboratory environment was controlled with a 12 h light and 12 h dark cycle, and the rats had unrestricted access to a standard pellet diet and water. The temperature in the animal house was kept at 23 ± 2°C, and the relative humidity was maintained at 50 ± 15%. The animals were given a seven-day period to acclimate. Ethical approval was secured from the Institutional Animal Ethical Committee (IAEC) (Approval No: IU/IAEC/19/20) at Integral University, Lucknow.

2.3 Induction of diabetes

Rats were kept without food but had access to water starting the previous evening. Streptozotocin (STZ) was dissolved in a cold citrate buffer (pH 4.5, 0.1 M) and administered intraperitoneally at a dose of 65 mg/kg body weight within 5 min. This was followed by an intraperitoneal injection of NIC (110 mg/kg) 15 min later. Blood glucose levels were measured 72 h post-injection. To prevent death from hypoglycemia, diabetic rats were provided with water and 5% glucose 24 h after the STZ injection. Blood samples were collected from the tail vein 72 h later and analyzed using a glucometer (Accu-Chek). Animals with plasma glucose levels exceeding 250 mg/dl were classified as diabetic and included in the diabetic studies.

To assess the impact of saxagliptin (5 mg/kg) combined with caffeic acid (40 mg/kg) on STZ-induced diabetic rats, diabetic animals were utilized post-induction. SD rats were organized into five groups, each containing five animals, and their initial body weights were documented. The treatment spanned 15 days for each group (Table 1). Upon conclusion of the study, the final body weights of all animals were measured. Subsequently, the animals were anesthetized using thiopentone sodium, and blood samples were obtained via retro-orbital puncture to measure blood sugar and other biochemical parameters.

Table 1: Treatment schedule

Groups (n=5)	Treatment	Dosage, route of administration and duration
1 (NC)	Vehicle (normal saline)	10 ml/kg, p.o. once a day for 15 days
2 (DC)	STZ + Nicotinamide	65 mg/kg, i.p. STZ (single dose) + 15 min after STZ, Nicotinamide (NIC) 110 mg/kg, i.p.
3 (SXG)	Diabetic rat + Saxagliptin	10 mg/kg, p.o. once a day for 15 days
4 (DC + CA)	Diabetic rat + Caffeic acid	40 mg/kg, p.o. once a day for 15 days
5 (SXG + CA)	Diabetic rat + Saxagliptin + Caffeic acid	5 mg/kg + 40 mg/kg, p.o. once a day for 15 days

(N = Number, NC = Normal control, DC = Diabetic control, STD = Standard, i.p. = intraperitoneal, STZ = Streptozotocin, p.o. = per oral, SXG = Saxagliptin).

2.4 Blood glucose estimation

At initial and final day of the treatment blood sugar measurements were taken by using tail's vein blood (by ACCUCHEK- ACTIVE kit made by Roche, Germany).

2.5 Oral glucose tolerance test

To assess glucose tolerance, an OGTT was conducted. Following a night of fasting, a dextrose solution (40% wt/vol.) was administered intra-gastrically to rats at a dosage of 2.5 g/kg of body weight, and blood glucose levels were measured at 0, 30, 60, and 120 min. Glucose levels were evaluated at these specific time intervals. The glucose tolerance (OGTT) was determined by calculating the area under the curve (AUC) for glucose using the trapezoidal method (Subramanian *et al.,* 2008).

AUC = (basal glycaemia + glycaemia 0.5 h) × 0.25 + (glycaemia 0.5 h + glycaemia 1 h) × 0.25 + (glycaemia 1 h + glycaemia 2 h) × 0.5.

2.6 Estimation of antioxidant level

The levels of antioxidants such as glutathione (GSH), glutathione peroxidase (GPx), catalase, glutathione, catalase activity, superoxide dismutase (SOD), and thiobarbituric acid reactive substances (TBARS) (MDA) were measured in pancreatic tissue (Jollow *et al.,* 1974; Marklund and Marklund, 1974; Ohkawa *et al.,* 1979; Claiborne, 1985).

2.7 Statistical analysis

The data is presented as the mean ± SEM for each group of four animals. Statistical analysis was conducted using one-way ANOVA, followed by Dunnett's test to compare all groups against the control (Graph Pad Instat, USA).

3. Results

3.1 Effect of saxagliptin with caffeic acid on the blood glucose level

In the diabetic control group (DC), glucose levels showed a significant rise ($p<0.0001$) compared to the normal control group (NC). Conversely, all treated groups exhibited a notable reduction in glucose levels ($p<0.0001$) when compared to the diabetic control (Table 2). Notably, the combination of saxagliptin (5 mg/kg) with caffeic acid (40 mg/kg) led to a more pronounced decrease ($p<0.001$) in glucose levels than saxagliptin (10 mg/kg) alone (Table 2).

3.2 Effect of saxagliptin with caffeic acid on the oral glucose tolerance (OGT)

In the diabetic control group (DC), the area under the curve (AUC) showed a significant increase ($p<0.0001$) compared to the normal control group (NC). Conversely, the AUC was notably reduced ($p<0.001$) across all treated groups when compared to the diabetic control. Notably, the combination treatment of saxagliptin (5 mg/kg) with caffeic acid (40 mg/kg) resulted in a more pronounced decrease ($p<0.001$) in AUC than saxagliptin (10 mg/kg) alone (Table 2).

Table 2: Effect of saxagliptin with caffeic acid on the blood glucose level and OGT

Groups	Treatment	Blood glucose level (mg/dl)	OGT (mg/dl)
1	NC	118.75 ± 4.53	9.37 ± 0.50
2	DC	314.0 ± 6.48####	37.94 ± 1.86####
3	SXG (10 mg)	168.0 ± 3.80****	18.57 ± 1.19***
4	(DC + CA 40 mg/kg)	198.49 ± 4.25****	27.75 ± 4.46*
5	SXG 5 mg/kg + CA 40 mg/kg	152.75 ± 2.05****[a]	10.16 ± 0.58****[a]

All values are expressed as mean ± SEM. The comparison was done by ANOVA followed by Dunnett's test. #### $p<0.0001$= Significant when compared NC, *$p<0.05$, ***$p<0.001$ and **** $p<0.0001$= Significant when compared diabetic control. [a]$p<0.001$ = Significant when compared with saxagliptin.

3.3 Effect of saxagliptin with caffeic acid on total protein level

In the diabetic control group (DC), the total protein level showed a significant reduction ($p<0.01$) compared to the normal control group (NC) (Table 3). Conversely, the total protein level significantly rose ($p<0.01$) in all treated groups when compared to the diabetic control. Notably, there was a significant increase ($p<0.01$) in the group treated with a combination of saxagliptin (5 mg/kg) and caffeic acid (40 mg/kg) compared to the group treated with saxagliptin (10 mg/kg) alone (Table 3).

Table 3: Effect of saxagliptin with caffeic acid on SOD level in pancreas tissue

Groups	Treatment	Total protein level	SOD level (µg/mg of protein)	MDA level (nmol/mg protein)	GSH level (µg/mg of protein)	Catalase level (U/mg of protein)
1	NC	2.163 ± 0.038	12.21 ± 0.38	0.84 ± 0.02	28.35 ± 0.28	11.12 ± 0.44
2	DC	1.108 ± 0.035####	4.87 ± 0.43####	1.32 ± 0.033####	7.50 ± 0.18####	4.73 ± 0.64####
3	SXG (10 mg)	1.255 ± 0.037*	7.18 ± 0.36**	0.93 ± 0.04****	10.77 ± 0.25****	8.17 ± 0.36**
4	(DC + CA 40 mg/kg)	1.175 ± 0.038ns	6.44 ± 0.25*	1.13 ± 0.08*	9.41 ± 0.30**	7.05 ± 0.41*
5	SXG 5 mg/kg + CA 40 mg/kg	1.560 ± 0.021****[a]	9.16 ± 0.39****[a]	0.726 ± 0.011****[a]	16.22 ± 0.40****[a]	10.37 ± 0.74****[a]

All values were expressed as mean ± SEM. ####$p<0.0001$=Significant, when compared with normal control (NC), *$p<0.01$=Significant and ****$p<0.0001$=Significant when compared with diabetic control (DC), [a]$p<0.001$=Significant when compared with saxagliptin.

3.4 Effect of saxagliptin with caffeic acid on SOD level in pancreas tissue

In the diabetic control group (DC), there was a significant reduction in SOD levels ($p<0.0001$) compared to the normal control group (NC). All treated groups showed a significant increase in SOD levels ($p<0.001$) when compared to the diabetic control (DC). Notably, the combination treatment of saxagliptin (5 mg/kg) with caffeic acid (40 mg/kg) resulted in a significantly higher increase ($p<0.001$) in SOD levels compared to saxagliptin (10 mg/kg) alone (Table 3).

3.5 Effect of saxagliptin with caffeic acid on MDA level in pancreas

In the diabetic control group (DC), the MDA level showed a significant increase ($p<0.0001$) compared to the normal control group (NC). When compared to the diabetic control (DC), all treated groups exhibited a significant reduction in MDA levels ($p<0.001$). Notably, the combination of saxagliptin (5 mg/kg) with caffeic acid (40 mg/kg) resulted in a more pronounced decrease ($p<0.001$) than saxagliptin (10 mg/kg) alone (Table 3).

3.6 Effect of saxagliptin with caffeic acid on GSH level in pancreas tissue

In the diabetic control group (DC), there was a significant reduction in GSH levels ($p<0.0001$) compared to the normal control group (NC). All treated groups showed a notable increase in GSH levels ($p<0.001$) when compared to the diabetic control (DC). Notably, the combination treatment of saxagliptin (5 mg/kg) with caffeic acid (40 mg/kg) resulted in a significantly higher increase ($p<0.001$) in GSH levels compared to saxagliptin (10 mg/kg) alone (Table 3).

3.7 Effect of saxagliptin with caffeic acid on catalase level in pancreas tissue

In the diabetic control group (DC), there was a significant reduction in catalase levels ($p<0.0001$) compared to the normal control group (NC). When compared to the diabetic control (DC), all treated groups showed a significant increase in catalase levels ($p<0.001$). Notably, the combination treatment of saxagliptin (5 mg/kg) with caffeic acid (40 mg/kg) resulted in a significantly higher increase ($p<0.001$) than saxagliptin (10 mg/kg) alone (Table 3).

4. Discussion

Diabetes mellitus (DM) is classified as a metabolic disorder, primarily characterized by prolonged elevated blood sugar levels. It is considered one of the world's most prevalent diseases, affecting a significant portion of the global population, and is divided into two main types: I and II. Complications arising from diabetes can include potential blindness, lower limb amputation, kidney failure, and the risk of heart attack or stroke (Anwar *et al.,* 2024).

Saxagliptin is a medication taken orally to reduce blood sugar levels in individuals with type 2 diabetes. It is part of the dipeptidyl peptidase-4 (DPP-4) inhibitor category. Both saxagliptin and its active metabolite, M2, which is half as potent as the original drug, function as DPP-4 inhibitors. They enhance glycemic control by preventing the breakdown of incretin hormones, specifically GLP-1 and glucose-dependent insulinotropic polypeptide. This action results in elevated GLP-1 levels, increased insulin secretion, and decreased levels of glucagon and glucose after meals (Li *et al.,* 2021).

The current research investigated the antidiabetic effects of saxagliptin combined with caffeic acid in a diabetic rat model. Caffeic acid was found to significantly reduce fasting blood glucose levels, aligning with findings from Celik *et al.,* 2009. Recent studies have indicated that caffeic acid lowers blood glucose levels and enhances insulin secretion in diabetic rats. It achieves this by inhibiting glucose-6-phosphatase activity, which affects hepatic glucose production and boosts glucokinase (GK) activity in the liver. Hepatic GK plays a crucial role in maintaining glucose balance and is a promising target for treating type 2 diabetes pharmacologically. An increase in hepatic GK can lead to greater utilization of blood glucose for energy production or glycogen storage in the liver (Sharma *et al.,* 2022).

This research found that saxagliptin led to weight gain in diabetic rats, which aligns with the findings of Nauck *et al.,* (2007) who explored the antidiabetic effects of various saxagliptin doses and observed an increase in body weight among diabetic rats.

The current research demonstrated that saxagliptin effectively reduced blood glucose levels in diabetic rats. Additionally, this study found that saxagliptin increased catalase levels in diabetic rats, consistent with the study by Mandlem *et al.,* (2017) which reported a similar increase in catalase levels due to saxagliptin. In another study, saxagliptin exhibited antioxidant properties, significantly lowering MDA levels in the STZ rat model of diabetes. In the present study, it also displayed antioxidant effects, significantly raising GSH levels and reducing MDA levels in pancreatic tissues. Furthermore, the combination of saxagliptin with caffeic acid resulted in better weight gain, normalized blood glucose levels, increased GSH, catalase, and SOD levels, and decreased MDA levels in diabetic rats compared to saxagliptin alone.

5. Conclusion

The present study investigated the antidiabetic effects of saxagliptin alone and in combination with caffeic acid in streptozotocin (STZ)-induced diabetic rats. The combination treatment significantly decreased blood glucose levels, improved oral glucose tolerance, increased body weight, total protein levels, and enhanced antioxidant status in pancreatic tissue compared to saxagliptin alone. The results suggest that the combination of saxagliptin and caffeic acid exerts superior antidiabetic effects, possibly through the mitigation of oxidative stress in pancreatic tissue, providing evidence for potential therapeutic benefits in managing type 2 diabetes mellitus.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Mohd Muzahid: Contributed to investigation, data curation, and methodology; **Badruddeen**: Contributed to conceptualization, supervision, project administration, validation, and overall guidance of the study; **Mohammad Irfan Khan**: Contributed to methodology and formal analysis; **Juber Akhtar**: Contributed to investigation and data curation; **Anas Islam**: Contributed to software handling, data analysis, and visualization of results; **Mohammad Ahmad**: Contributed to resources and critical review of the manuscript; **Mohd Muazzam Khan**: Contributed to writing the original draft, reviewing, and editing of the manuscript; **Usama Ahmad**: Contributed to investigation and validation of experimental data; **Mohd Munazir**: Contributed to validation, critical revision, and final approval of the manuscript; **Rabiya Ahsan**: Contributed to literature survey and drafting of the manuscript.

Consent for publication

All authors gave their full consent for publication and submission to this journal.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

Funding

The authors stated that the work presented in this article received no associated funding.

Ethics approval

Approved by the Institutional Animal Ethics Committee (IAEC), Protocol No: IU/IAEC/19/20.

Acknowledgements

The authors acknowledge the Department of Pharmacy, Faculty of Pharmacy, Integral University, Lucknow Uttar Pradesh India, for providing institutional support, infrastructure facilities, and access to academic resources essential for the successful completion of this research work.

References

Anwar, K. R.; Badruddeen; Akhtar, J.; Khan, M. I. and Ahmad, M. (2024). An outlook on pathological pathways of diabetes and molecular mechanisms of anti-diabetic phytobioactives. Lett. Funct. Foods, **1**(1): e180723218858.

Boulton, D. W. (2017). Clinical pharmacokinetics and pharmacodynamics of saxagliptin, a dipeptidyl peptidase-4 inhibitor. Clin. Pharmacokinet., **56**(1):11-24.

Celik, S.; Erdogan, S. and Tuzcu, M. (2009). Caffeic acid phenethyl ester (CAPE) exhibits significant potential as an antidiabetic and liver-protective agent in streptozotocin-induced diabetic rats. Pharmacol. Res., **60**(4):270-276.

Claiborne, A. L. (1985). Catalase activity. In: Handb. Methods Oxygen Radical Res., 383.

Deacon, C. F. (2018). Peptide degradation and the role of DPP-4 inhibitors in the treatment of type 2 diabetes. Peptides, **100**:150-157.

Hashim, M.; Badruddeen; Akhtar, J.; Khan, M. I.; Ahmad, M.; Islam, A. and Ahmad, A. (2024). Diabetic neuropathy: an overview of molecular pathways and protective mechanisms of phytobioactives. Endocr. Metab. Immune Disord. Drug Targets, **24**(7):758-776.

Hashim, M.; Badruddeen; Akhtar, J.; Khan, M. I.; Ahmad, M.; Islam, A.; Ahmad, A. and Zahra, F. (2023). Diabetic nephropathy: an outline on molecular mechanism and protective pathways of phytoconstituents. J. Phytonanotech. Pharmaceut. Sci., **3**(3):1-16.

Jollow, D. J.; Mitchell, J. R.; Zampaglione, N. A. and Gillette, J. R. (1974). Bromobenzene-induced liver necrosis: protective role of glutathione and evidence for 3,4-bromobenzene oxide as the hepatotoxic metabolite. Pharmacology, **11**(3):151-169.

Li, G.; Yi, B.; Liu, J.; Jiang, X.; Pan, F.; Yang, W.; Liu, H.; Liu, Y. and Wang, G. (2021). Effect of CYP3A4 inhibitors and inducers on pharmacokinetics and pharmacodynamics of saxagliptin and active metabolite M2 in humans using physiological-based pharmacokinetic combined DPP-4 occupancy. Front. Pharmacol., **12**:746594.

Mandlem, V. K. K. and Annapurn, A. (2017). Cardioprotective role of saxagliptin through antioxidant mechanism in experimental myocardial infarction in streptozotocin-induced diabetic rats. Clin. Exp. Pharmacol., 7:233.

Marklund, S. and Marklund, G. (1974). Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. Eur. J. Biochem., **47**(3):469-474.

Nauck, M.; Meininger, G.; Sheng, D. O.; Terranella, L.; Stein, P. P. and Sitagliptin Study 024 Group (2007). Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin compared with the sulfonylurea glipizide in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes. Metab., **9**(2):194-205.

Ohkawa, H.; Ohishi, N. and Yagi, K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal. Biochem., **95**(2):351-358.

Sharma, P.; Singh, S.; Sharma, N.; Singla, D.; Guarve, K. and Grewal, A. S. (2022). Targeting human glucokinase for the treatment of type 2 diabetes: an overview of allosteric glucokinase activators. J. Diabetes Metab. Disord., **21**(1):1129-1137.

Shoaib, A.; Salem-Bekhit, M. M.; Siddiqui, H. H.; Dixit, R. K.; Bayomi, M.; Khalid, M.; Badruddeen and Shakeel, F. (2020). Antidiabetic activity of standardized dried tubers extracts of *Aconitum napellus* in streptozotocin-induced diabetic rats. 3 Biotech, **10**(2):56.

Singh, H.; Singh, R.; Singh, A.; Singh, H.; Singh, G.; Kaur, S. and Singh, B. (2024). Role of oxidative stress in diabetes-induced complications and their management with antioxidants. Arch. Physiol. Biochem., **130**(6):616-641.

Vuolo, M. M.; Lima, V. S. and Junior, M. R. (2019). Phenolic compounds: structure, classification, and antioxidant power. In: Bioactive Compounds, Woodhead Publishing, pp: 33-50.

Yusuf, M.; Nasiruddin, M.; Sultana, N.; Akhtar, J.; Khan, M. I. and Ahmad, M. (2019). Regulatory mechanism of caffeic acid on glucose metabolism in diabetes. Res. J. Pharm. Technol., **12**(10):4735-4740.

Citation **Mohd Muzahid, Badruddeen, Mohammad Irfan Khan, Juber Akhtar, Anas Islam, Mohammad Ahmad, Mohd Muazzam Khan, Usama Ahmad, Mohd Munazir and Rabiya Ahsan (2025). Comparative evaluation of saxagliptin alone and in combination with caffeic acid in STZ-induced diabetes in rats. J. Phytonanotech. Pharmaceut. Sci., 5(4):57-61. http://dx.doi.org/10.54085/jpps.2025.5.4.7**